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(54) Title: DEVICE FOR ADMINISTRATION OF BENEFICIAL MATERIALS TO RUMINANTS

(57) Abstract

The invention described is a bolus for the controlled release of a beneficial agent in the rumen of a ruminant animal. The bolus consists in a core containing a binder, solubilising agent, the beneficial agent to be released and, when required, a densifier. The core is coated with a wax coating, preferably with an opening exposing a small part of the core to rumen juices. The core is gradually dissolved releasing the beneficial agent. As the core dissolves the wax coating erodes until the bolus disappears completely.

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DEVICE FOR ADMINISTRATION OF BENEFICIAL MATERIALS TO RUMINANTS

TECHNICAL FIELD

This invention relates to a controlled release device. More particularly, it relates to a bolus for releasing beneficial substances into the rumens of ruminants.

BACKGROUND ART

Slow release devices or boluses are well known in the art. In GB 2,122,086 there is described a bolus having a compressed core containing an active ingredient and a skin of brittle material. The core is exposed to the rumen fluids and gradually disintegrates. The brittle skin which is supported by the core breaks away as the support disappears. The core is made of dry mixed materials which are compressed together. It is difficult to compress a core of uniform density. If the core is not homogeneous in its density there is an uneven distribution of material during disintegration which can be a disadvantage if the beneficial material has to be dispensed at particular rates.

US patent 3,535,419 describes a bolus having three separate components:

a) one or more highly water insoluble materials such as a solid wax, fat, oil, fatty acid amide, ester or alcohol or polymer;

b) a high density non-toxic metal derivative; and

c) a therapeutic agent.

Its method of operation is by disintegration of the composition and leaching out of the active ingredient. The rate of dissolution is determined by the degree of compression.

It is an object of the present invention to go some way towards overcoming the disadvantages of the prior art or at least to offer the public a useful choice.

DISCLOSURE OF THE INVENTION

Accordingly, the invention may be said broadly to consist in a bolus which comprises:

i) a core comprising a substantially homogeneous mixture of:

a) a water soluble physiologically acceptable binder comprising wax, fat, oil, fatty acid, fatty acid ester, fatty acid amide, fatty acid alcohol or the like organic compound having a melting point above 50°C;

b) a physiologically acceptable solubilising agent;

c) a beneficial agent; and

d) where required, a physiologically acceptable inert densifier of sufficient density and in sufficient quantities to give the bolus a minimum density of 1.5 g/cm^3; and

ii) a coating of a physiologically acceptable wax over substantially all of the surface of the core but leaving exposed a core portion whereby in use liquid in the rumen will dissolve said core allowing release of the beneficial agent into the rumen.

Preferably said binder comprises a fatty acid ester.

Preferably said fatty acid ester is glycerol monostearate.

Preferably said solubilising agent is polyethylene glycol stearate.

Alternatively, said solubilising agent is a sodium salt of a long chain fatty acid.

Preferably said beneficial agent is a nutrient.

Alternatively said beneficial agent is a growth promotant.

Alternatively, said beneficial agent is a therapeutic substance.

Alternatively, said beneficial agent is mixture of a nutrient and a therapeutic substance.

Preferably said beneficial agent is zinc oxide.

Preferably said densifier is iron powder, barium sulphate or iron oxide.

Preferably said bolus is in the shape of a cylinder which is closed at one end and open at the other.

Preferably said closed end is hemispherical in shape.

In an alternative construction, said core is cylindrical and consists in alternating cylindrical layers, each alternate layer containing all of the ingredients of the core except the beneficial agent whereby the beneficial agent is released in separate doses.

Preferably said bolus is as herein described with reference to the drawings.

In another embodiment the invention may be said broadly to consist in a method of making a bolus which comprises:

a) melting a mixture of a water insoluble physiologically acceptable binder comprising wax, fat, oil, fatty acid, fatty acid ester, fatty acid amide, fatty acid alcohol or the like organic compound having a melting point above 50°C; a physiologically acceptable solubilising agent; a beneficial agent; and where required, sufficient physiologically acceptable inert filler material of sufficient density to give the bolus a minimum density of 1.5 g/cm^3;

b) mixing said mixture until it is substantially homogeneous;

c) dividing said substantially homogeneous mixture into predetermined dosages; and

d) coating said dosages with a physiologically acceptable wax.

Preferably said substantially homogeneous mixture is extruded and cut into predetermined dosage lengths.

Alternatively said substantially homogeneous mixture in the form of a melt is poured into a mould of predetermined dosage volume and allowed to solidify.

In another alternative process said binder and said solubilising agent are dissolved in a physiologically acceptable solvent and said solvent is allowed to evaporate from said dosages into which said mixture has been divided prior to said coating step.

Preferably said coating step comprises coating all but a small area of each said dosage length.

Preferably each said dosage is in the form of a cylinder and said coating step comprises coating all but one end thereof.

This invention may also be said broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, and any or all combinations of any two or more of said parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which this invention relates, such known equivalents are deemed to be incorporated herein as if individually set forth.

The invention consists in the foregoing and also envisages constructions of which the following gives examples.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention may also be understood by having reference to the accompanying drawings in which:

Figures 1A, 1B and 1C are cross-sectional elevations of a first embodiment of a bolus according to the invention showing the mode of release of beneficial agent.

Figure 2 is a cross-sectional elevation of a second embodiment of a bolus according to the invention showing alternative active and inert core layers.

Figure 3 is a cross-sectional elevation of another embodiment of a bolus according to the invention in which beneficial agent is stored in transverse cavities or grooves in the core.

Figure 4 is an elevation of another embodiment of a bolus according to the invention in which beneficial agent is present in longitudinal bores in the core surface just below the outer coating.

Figure 5 is a cross-sectional elevation of another embodiment of a bolus according to the invention in which beneficial agent is present in a longitudinal bore within the core of the bolus.

Figure 6 is a plot of percentage of controls showing facial eczema against percentage protection afforded by a four week bolus.

Figure 7 is a plot of percentage of controls showing facial eczema against percentage protection afforded by a six week bolus.

MODES OF CARRYING OUT THE INVENTION

The bolus illustrated in figure 1 comprises a core 12 coated by a wax coating 10. The coating 10 is closed at one end 13 and open at the other 14. The closed end 13 may be hemispherical in shape or have a substantially flat bottom as illustrated. The open end 14 of the wax coating allows the core 12 to be exposed to the juices in the rumen. As illustrated in figure 1B, the juices in the rumen gradually dissolve the core 12 releasing particles 16 of active agent. As the core is dissolved the open end of the wax coating 10 simultaneously erodes so that the bolus as illustrated in figure 1C becomes progressively shorter until it has disintegrated completely.

In figure 2 the bolus is identical to the one illustrated in figure 1A except that instead of being provided with a homogeneous core it is provided with a core consisting of alternating layers 18 and 20. Layer 18 consists of all of the filler materials and includes the beneficial agent as described below. Layer 20 contains only the filler materials and no beneficial agent. The bolus illustrated in figure 2 is gradually dissolved and eroded in the same way as that illustrated in figures 1A to 1C but the beneficial ingredient is leached out at spaced intervals. Such a bolus would be used where beneficial agents such as medicaments are to be administered in pulsed dosages. The length of time between administration of doses can be controlled by the thickness of the inert layers 20.

The bolus in figure 3 is intended to dispense beneficial agents in pulsed dosages as well. The core 12 contains all of the inert ingredients, that is the binding agent, solubilising agent and densifier if necessary. The core 12 is provided with either bores 22 extending transversely through the core, or circumferential rings or grooves 24. The bores 22 or grooves 24 contain the beneficial agents 23 or 25, respectively, in a concentrated form. The core and bore or grooves are coated with wax in the same manner as for the other embodiments. As the wax coating erodes the beneficial ingredient 23 or 25 is released in dosage pulses as it is exposed to the rumen juices.

As shown in figure 4 beneficial agent may also be placed in longitudinal grooves 23 cut in the surface of core 12. The filled grooves are then coated with wax coating 10 along with the rest of core 12.

As shown in figure 5 a beneficial agent may be placed in longitudinal bore 27 as well.

PRODUCTION METHOD

The cores according to the invention may be produced by either extrusion or by pouring and allowing either the melted binding agent to solidify or allowing solvent to evaporate as the case may be.

All of the ingredients except the wax outer coating are mixed together. Where no solvent is used the mixture is heated to melt the binding agent and then stirred into a substantially homogeneous mixture. If a moulding method is used the mixture is poured into moulds having the shape of the cores of the drawings and allowed to cool. The cores are then released from the mould and coated with the wax either by dipping or pouring the wax over the core. If a solvent is used the binding agent is dissolved in the solvent rather than being melted and the solvent is allowed to evaporate.

When an extruder is used the mixture of ingredients is allowed to cool or the solvent allowed to evaporate into the form of a semi-solid paste. The extruded material is cut into appropriate dosage lengths. When a core of the construction shown in figure 2 is to be made a pair of extruders are run next to one another. One extruded mixture contains no beneficial agent. The other one contains the beneficial agent in the desired dosage form. The extrusions are then cut into relatively short lengths as illustrated in figure 2 and placed together in alternating active and inert layers and coated as described above.

When producing the core illustrated in figure 3 an extrusion containing all but the beneficial ingredient and cut to lengths is then drilled by a series of drills operating in parallel or else grooved using a router and rotating device to produce either the bores 22 through the core or the grooves 24 around the core. Beneficial agent 23 in a substantially melted form is then poured into the bores 22 and the core is then coated with waxes described above. In order to keep the active ingredient from within the core the drills producing bores 22 are positioned so as to not pass completely through the bottom of the core beneath them. When grooves 24 are used beneficial ingredient in the form of a paste 23 is extruded into the grooves and the core coated in the usual way. Longitudinal grooves 23 and longitudinal bores 27 (see figures 4 and 5) are formed and filled with beneficial agent in a similar manner.

ALTERNATIVE FORMULATIONS

The binding agent for the core can be any physiologically acceptable water insoluble component which can be formed into a substantially homogeneous mixture with the solubilising agent, the beneficial agent and the densifying agent. Most preferably the binding agent will be one which can be melted at temperatures not

deleterious to the other components or one which is soluble in solvents which can be evaporated to allow the core to solidify. Any solvent used would have to be physiologically acceptable to the animal being fed the bolus. Suitable binding agents are those exemplified in United States patent 3,535,419. We have found that glycerol monostearate is a particularly suitable binding agent.

The solubilising agent works in conjunction with the binding agent in the rumen environment in a manner not completely understood. However, it is believed that the solubilising agent together with the gastric juices gradually dissolve the binding agent in the core.

In the embodiment described in the following example the beneficial agent is zinc oxide. Zinc oxide has a sufficient density that it is not necessary to include a high density inert material to weight the bolus down so that it is not disgorged from the rumen.

Persons skilled in the art will be aware of other beneficial ingredients which can be administered through use of this bolus. This can include additional nutrients where these are necessary and other therapeutic agents for the treatment of parasites, diseases or other afflictions of ruminants.

In order to avoid the bolus being regurgitated from the rumen, it preferably has a minimum density of 1.5 g/cm^3. More preferably the density is 2.5 g/cm^3. With many therapeutic agents other than zinc oxide it will be necessary to include densifying substances. These should be inert and physiologically acceptable to the animal intended to ingest the bolus. The density of the densifier should be sufficient to give the desired minimum density to the entire bolus.

A wide variety of waxes may be used. A mixture of paraffin wax and of carnauba wax or a mixture of bees wax and carnauba wax have been found to be successful. The wax used will need to be physiologically acceptable to the animal intended to ingest it and be of such a composition that it erodes at the open end under the conditions within the rumen.

EXAMPLE 1: Preparation of a bolus containing zinc oxide

A mixture containing 83.5% zinc oxide and 16.5% glycerol monostearate was melted and mixed. The glycerol monostearate contained 75 to 90% EMULDAN HS40 (a trade name for glycerol monostearate non-self-emulsifying) and 10 to 25% LIPOMULSE 165 (a trade name for glycerol monostearate self-emulsifying, which is a blend of glycerol monostearate and polyethylene glycol monostearate). The mixture was then extruded and core lengths cut to predetermined dosage lengths and coated with a wax. The wax consisted of 25% carnauba wax and 75% paraffin wax.

EMULDAN HS40 was obtained from Grindsted Products A/S of Brabrand, Denmark and LIPOMULSE 165 from Lip Chemicals Inc, of Paterson, New Jersey, USA. All of the percentages are by weight of the core mixture or of the wax coating.

EXAMPLE 2: Boluses with Different Release Times

(a) Four Week Release Time

A bolus was prepared as in example 1. The glycerol monostearate comprised 80% non-self-emulsifying glycerol monostearate (EMULDAN HS40) and 20% self-emulsifying glycerol monostearate (LIPOMULSE 165).

It was found that a bolus containing 43 gm of zinc oxide was fully dissolved and eroded in sheep of weight ranges of 20 to 40 kg on average in about four weeks.

(b) Six Week Release Time

A bolus was prepared as in example 1. The glycerol monostearate comprised 85% non-self-emulsifying glycerol monostearate (EMULDAN HS40) and 15% self-emulsifying glycerol monostearate (LIPOMULSE 165).

It was found that a bolus containing x gm of zinc oxide was fully dissolved and corroded in sheep of weight ranges of y to z kg on average in about 6 weeks.

EXAMPLE 3: Field Trials

Boluses for zinc administration to lambs containing the same amount of zinc were prepared in accordance with the method of examples 1 and 2. One released the zinc over a 4-week period, the other over 6 weeks. These devices were tested for their ability to prevent facial eczema (FE) in lambs on farms in Northland, Auckland, Waikato and Wanganui in New Zealand during the 1994 FE season. (February to March 1994).

Groups of approximately 50 lambs on 26 farms in these regions received one or other of the devices, which were renewed every 4 to 6 weeks until the end of the FE season. On farms where precautions against FE were normally taken, a control group was left untreated so that the protective effect of the devices could be assessed. On properties where no precautions were taken, a random-chosen group of lambs was used as control.

Blood samples were regularly taken from the control group for assay of -glutamyl transferase (GGT) activity, a measure of the liver damage caused by FE. When significant liver damage was detected in the control group, all the lambs were bled, and the severity of the liver damage categorised according to GGT activity (measured in international units) as follows:

<55	No eczema
55-150	Mild eczema
151-330	Moderate eczema
>330	Severe eczema

Facial eczema occurred on 15 of the farms under study. Some farms, were severely affected by FE during 1994, with more than 80% of the unprotected control lambs showing liver damage. On two farms, the outbreak was very prolonged, and a second blood sample taken in May showed a continuing severe challenge in the control lambs. Excellent protection was given by both devices, with less than 10% of the animals showing any signs of liver damage over the whole of the observation period. Good protection was also seen on the two other most affected farms, with both the incidence and severity of liver damage being greatly reduced.

A less severe challenge was seen on seven farms with between 40 and 65% of the control animals being affected. Again, excellent protection was given by the intraruminal devices, with the incidence of eczema being generally less than 20% and then only in the "mild" category.

Comparatively little eczema was recorded on the remaining four farms with an 18-38% incidence of liver damage. On these farms, the devices gave almost complete protection.

On one of the severely affected farms, lambs other than the controls were given zinc oxide by drench at fortnightly intervals throughout the FE season. A sample of these animals was bled on 11 May for comparison with the control lambs and those given the intraruminal devices. These data show that fortnightly dosing does decrease the incidence of facial eczema (90% in the control compared with 64% in the zinc-dosed animals) but it is nowhere near as effective as the zinc intraruminal devices, both of which reduced the incidence of eczema to less than 10%.

STATISTICAL ANALYSES

In the first analyses, the animals were divided into two groups - those that showed no eczema and those showing some sign of the disease, irrespective of its severity.

The overall means percentage of animals showing no eczema are shown in Table 1.

Table 1: Overall mean percentage of animals showing no eczema - all trials

	Mean percent without eczema
Control	41.4 ± 5.5
4-week device	88.8 ± 3.0 *
6-week device	91.4 ± 1.6 *

* Significantly different from the control value, $P<0.001$.

In order to establish the overall efficacy of the devices, the data from each farm was analysed by plotting the percentage of controls showing eczema against the percentage protection afforded, defined as the percentage of animals in the treated group without eczema less the percentage of animals in the control group without eczema.

These plots are shown in Figures 6 and 7 for the 4- and 6-week devices respectively. As expected, the lines pass through the origin in both cases; if there is no eczema, there can be no protection. The points are fitted to a straight line; from the slopes of these lines it can be predicted that 86±3% of animals in a flock would be protected by the 4-week device and 81±4% by the 6-week device. In simple terms, this indicates that if 100 control sheep were grazed on toxic pasture and 80 were affected, by a greater or lesser degree, with eczema, on average, only 11 of animals treated with the 4-week device and 15 of those treated with the 6-week device would show any sign of eczema.

Such an analysis does not, however, take into account the severity of the disease. A minor amount of liver damage is of little consequence in practical terms, and protection against moderate or severe eczema is of paramount importance. The data were therefore re-analysed, eliminating animals which suffered only mild eczema. From this analysis, it is predicted that 95±1% of animals in a flock would be protected from moderate or severe eczema by the 4-week device and 89±3% of animals by the 6-week device.

The results from these experiments show that the intraruminal devices consistently decrease the incidence and severity of facial eczema in grazing lambs under normal farming conditions, even after severe and prolonged challenge.

Although this invention has been described in relation to the controlled release of zinc to control facial eczema it will be appreciated by those skilled in the art that many other beneficial agents may be released by use of the bolus of this invention.

It will also be appreciated that the rate and timing of release is controlled by both the configuration of beneficial agent within the core and by the solubility of the core. The solubility can be altered by use of a greater or lesser proportion of solubilising agent.

CLAIMS:

1 A bolus which comprises:

i) core comprising a substantially homogeneous mixture of:

a) a water soluble physiologically acceptable binder comprising wax, fat, oil, fatty acid, fatty acid ester, fatty acid amide, fatty acid alcohol or the like organic compound having a melting point above 50°C;

b) a physiologically acceptable solubilising agent;

c) a beneficial agent; and

d) where required, a physiologically acceptable inert densifier of sufficient density and in sufficient quantities to give the bolus a minimum density of 1.5 g/cm^3; and

ii) a coating of a physiologically acceptable wax over substantially all of the surface of the core but leaving exposed a core portion whereby in use liquid in the rumen will dissolve said core allowing release of the beneficial agent into the rumen.

2 A bolus as claimed in claim 1 wherein said binder comprises a fatty acid ester.

3 A bolus as claimed in claim 1 or 2 wherein said fatty acid ester is glycerol monostearate.

4 A bolus as claimed in claim 1 or 2 wherein said solubilising agent is polyethylene glycol stearate.

5 A bolus as claimed in any one of claims 1 to 3 wherein said solubilising agent is a sodium salt of a long chain fatty acid.

6 A bolus according to any one of the preceding claims wherein said beneficial agent is a nutrient.

7 A bolus according to any one of claims 1 to 5 wherein said beneficial agent is a therapeutic substance.

8 A bolus according to claim 7 wherein said therapeutic substance is zinc oxide.

9 A bolus according to any one of claims 1 to 5 wherein said beneficial agent is a growth promotant.

10 A bolus according to any one of claims 1 to 5 wherein said beneficial agent contains both a nutrient and a therapeutic substance.

11 A bolus according to any one of the preceding claims wherein said densifier is iron powder, barium sulphate or iron oxide.

12 A bolus according to any one of the preceding claims which is in the shape of a cylinder which is closed at one end and open at the other.

13 A bolus as claimed in claim 12 wherein said closed end is hemispherical in shape.

14 A bolus as claimed in any one of the preceding claims wherein said core is cylindrical and consists in alternating cylindrical layers, each alternate layer containing all of the ingredients of the core except the beneficial agent whereby the beneficial agent is released in separate doses.

15 A method of making a bolus which comprises:

a) melting a mixture of a water insoluble physiologically acceptable binder comprising wax, fat, oil, fatty acid, fatty acid ester, fatty acid amide, fatty acid alcohol or the like organic compound having a melting point above 50°C; a physiologically acceptable solubilising agent; a beneficial agent; and where required, sufficient physiologically acceptable inert filler material of sufficient density to give the bolus a minimum density of 1.5 g/cm^3;

b) mixing said mixture until it is substantially homogeneous;

c) dividing said substantially homogeneous mixture into predetermined dosages; and

d) coating said dosages with a physiologically acceptable wax.

16 A method as claimed in claim 15 wherein said substantially homogeneous mixture is extruded and cut into predetermined dosage lengths.

17 A method as claimed in claim 15 wherein said substantially homogeneous mixture in the form of a melt is poured into a mould of predetermined dosage volume and allowed to solidify.

18 A method as claimed in claim 15 wherein said binder and said solubilising agent are dissolved in a physiologically acceptable solvent and said solvent is allowed to evaporate from said dosages into which said mixture has been divided prior to said coating step.

19 A method as claimed in any one of claims 15 to 18 wherein said coating step comprises coating all but a small area of each said dosage length.

20 A method as claimed in any one of claims 1 to 19 wherein said dosage is in the form of a cylinder and said coating step comprises coating all but one end thereof.

21 A method of administering a beneficial agent to a ruminant animal which comprises feeding said animal a bolus according to any one of claims 1 to 14.

FIG 1A

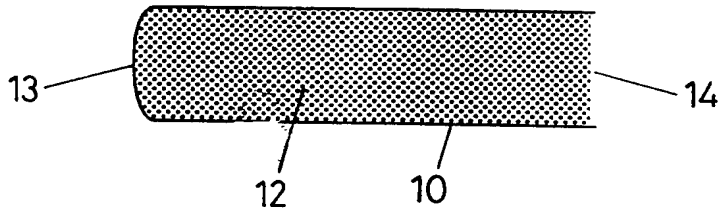


FIG 1B

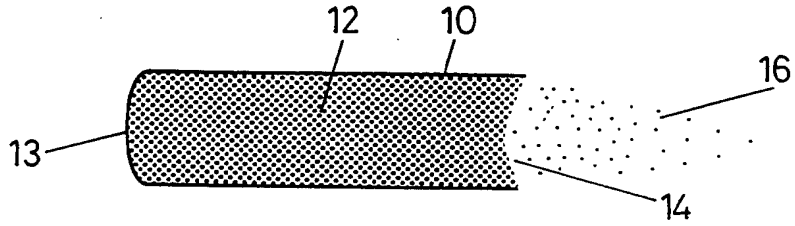


FIG 1C

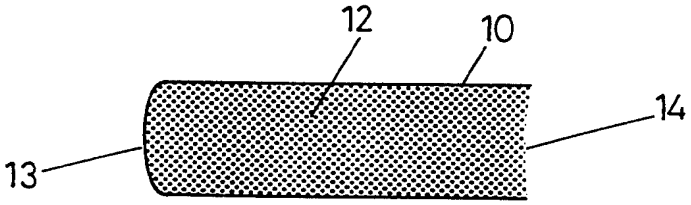


FIG 2

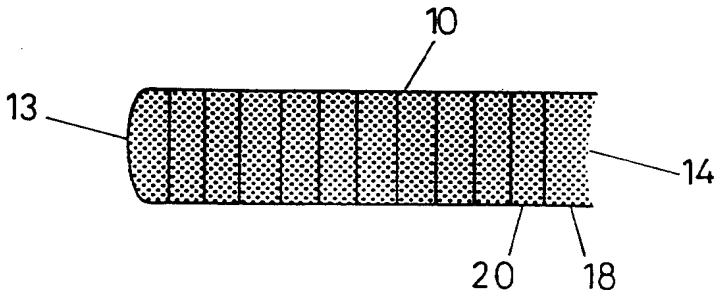


FIG 3

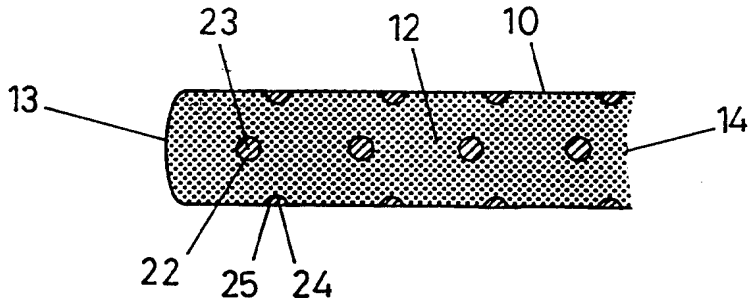


FIG 4

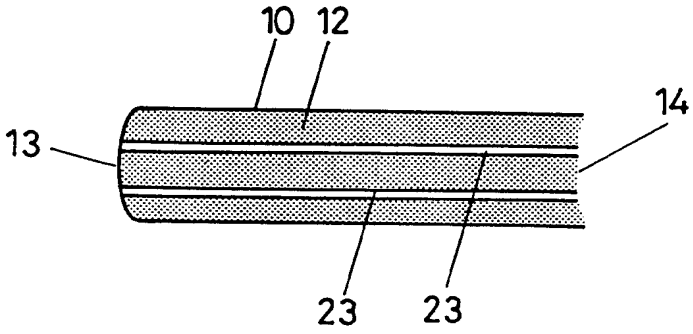


FIG 5

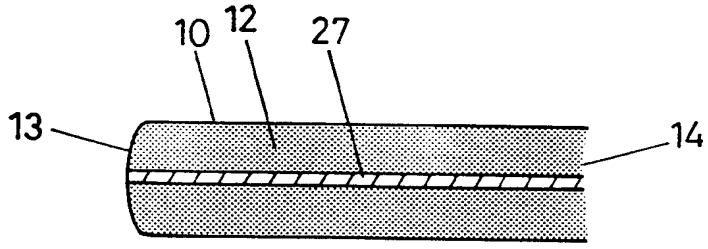


Fig. 6 Plot of percentage of controls showing eczema against percentage protection afforded by the 4-week device

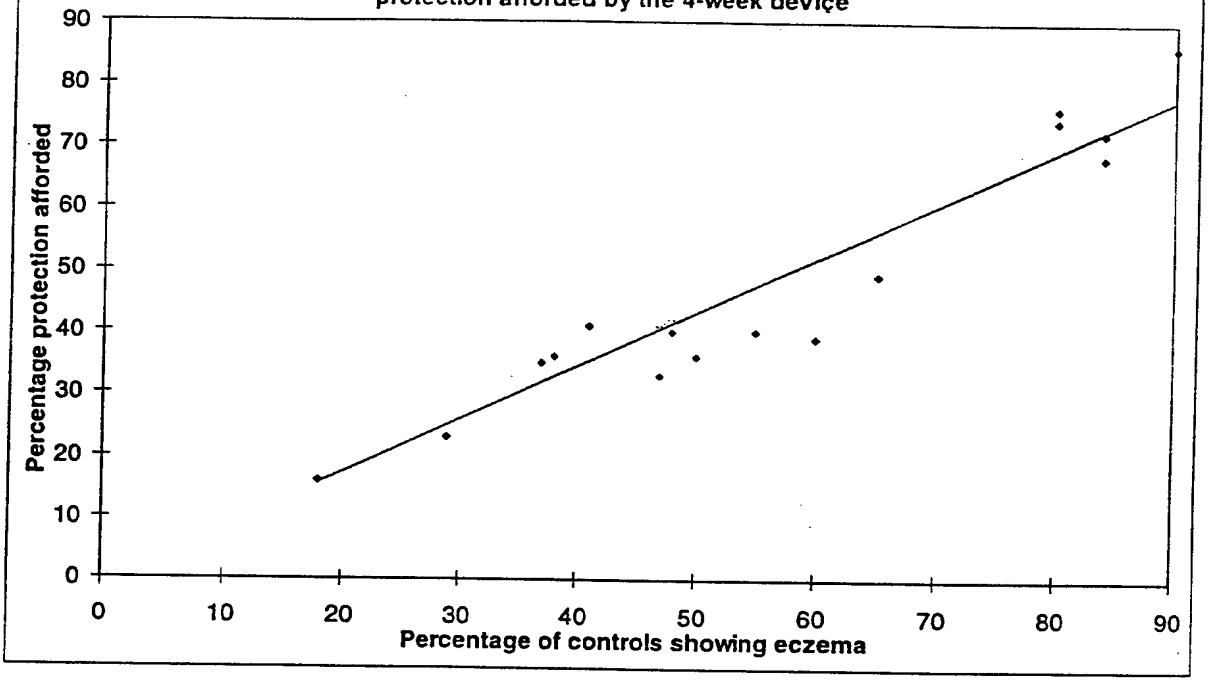
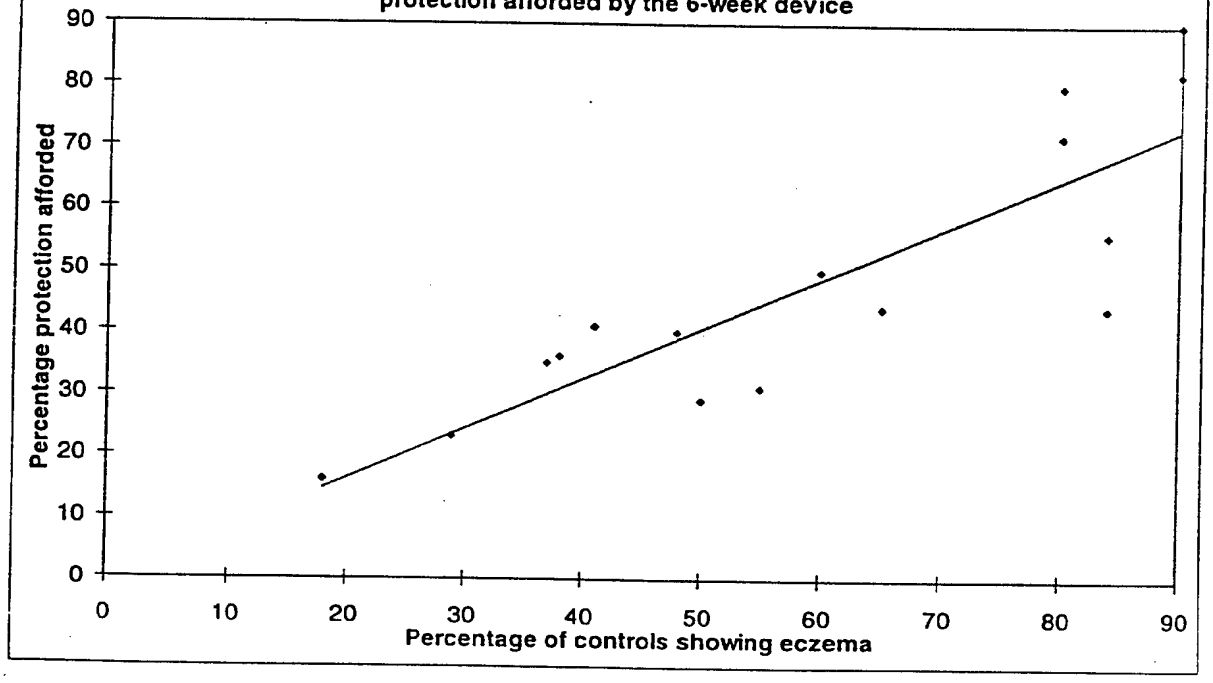


Fig. 7 Plot of percentage of controls showing eczema against percentage protection afforded by the 6-week device



INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 95/00005

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.[6] A61K 9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC : A61K 9/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
CASM : RUMEN, BOLUS.
WPAT : RUMEN, BOLUS.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	AU 50522/90 (AMERICAN CYNAMID COMPANY) 6 September 1990	1-21
A	EP 236002 (THE WELLCOME FOUNDATION LIMITED) 9 September 1987	1-21
A	US 4670248 (SCHRICKER) 2 June 1987	1-21
A	EP 220928 (STC plc) 6 May 1987	1-21
A	GB 2124899A (STANDARD TELEPHONES AND CABLES PUBLIC LIMITED COMPANY) 29 February 1984	1-21

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 1995	4 May 1995 (04.05.95)
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929	Authorized officer **J.P. PULVIRENTI** Telephone No. (06) 2832253

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 95/00005

C(Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
A	EP 062391 (RESEARCH CORPORATION) 13 October 1982	1-21
A	GB 2077103A (PITMANN-MOORE INC) 16 December 1981	1-21
A	US 4066754 (CHOU) 3 January 1978	1-21
A	US 4044119 (CARLSON Jr et al) 23 August 1977	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 95/00005

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	50522/90	JP	2267351	DC	2010934	DE	69007515
		EP	385106				
EP	236002	US	5322692	AU	68869/87	CA	1308354
		DE	3783923	EP	236002	GB	8603964
		NZ	219300				
US	4670248						
EP	220928	AU	64791/86	GB	8526124	US	4849001
		WO	8702657				
GB	2124899	AU	16712/83	NZ	204879		
EP	62391	AU	79582/82	CA	1182352	JP	57163310
		NZ	199424	US	4381780		
GB	2077103	AU	71002/81	US	4326522		
US	4066754	CA	1085727				
US	4044119	CA	1073357				

END OF ANNEX